to target nucleic acid sequence, wherein said virtual compounds modulate the expression of a target nucleic acid sequence;

synthesizing compounds corresponding to at least some of said virtual compounds; and

robotically assaying said synthetic compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

56. (Amended) A method of defining a set of compounds comprising:

evaluating *in silico* a plurality of virtual compounds according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

B1

58. (Amended) A method of defining a set of compounds comprising:

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generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

Sub C2

robotically assaying a plurality of synthetic compounds having at least some of said nucleobase sequences for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

59. (Amended) A method of defining a set of compounds comprising:

evaluating *in silico* a plurality of virtual compounds according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic compounds corresponding to at least some of said virtual compounds for one or more desired physical, chemical or biological properties.

60. (Amended) A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, wherein said oligonucleotides modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to defined criteria; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

B2

62. (Amended) A method of generating a set of oligonucleotides comprising:

B3

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides having at least some of said nucleobase sequences; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

63. (Amended) A method of generating a set of oligonucleotides comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

64. (Amended) A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

65. (Amended) A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) choosing an oligonucleotide chemistry;

c) robotically synthesizing a set of synthetic oligonucleotides having said nucleobase sequences of step a) and said oligonucleotide chemistry of step b);

d) robotically assaying said set of synthetic oligonucleotides of step c) for a physical, chemical or biological activity by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay; and

e) selecting a subset of said set of synthetic oligonucleotides of step c) having a desired level of physical, chemical or biological activity in order to generate said set of compounds.

66. (Amended) A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) and the oligonucleotide chemistry of b) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step c) and said oligonucleotide chemistry of step b);

e) robotically assaying said set of synthetic oligonucleotides of step (d) for a physical, chemical or biological activity by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay; and

f) selecting a subset of said set of synthetic oligonucleotides of step d) having a desired level of physical, chemical or biological activity in order to generate said set of oligonucleotides.

B3

67. (Amended) A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, wherein said oligonucleotides modulate the expression of a target nucleic acid sequence via binding of said oligonucleotides with said target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

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69. (Amended) A method of generating a set of oligonucleotides comprising:

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a) evaluating *in silico* a plurality of virtual oligonucleotides according to defined criteria, wherein said defined criteria is thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

70. (Amended) A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

71. (Amended) A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) and the oligonucleotide chemistry of b) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step c) and said oligonucleotide chemistry of step b);

e) robotically assaying said set of synthetic oligonucleotides of step (d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of synthetic oligonucleotides of step d) having a desired level of physical, chemical or biological activity in order to generate said set of oligonucleotides.

72. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

74. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic oligonucleotides having said nucleobase sequences for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

75. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.

78. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

79. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

80. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c);

e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and

f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity.

81. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically assaying a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

82. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

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b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically assaying a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties.

85. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides; and

c) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

86. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said plurality of virtual oligonucleotides; and

d) robotically assaying said plurality of synthetic oligonucleotides for one or more desired physical, chemical or biological properties.

87. (Amended) A method of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to said nucleic acid sequences comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) choosing an oligonucleotide chemistry;

c) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, and selecting those having preferred characteristics, in order to generate a set of preferred nucleobase sequences;

d) robotically synthesizing a set of synthetic oligonucleotides having said preferred nucleobase sequences of step b) and said oligonucleotide chemistry of step c);

e) robotically assaying said set of synthetic oligonucleotides of step d) for a physical, chemical or biological activity; and

B7 f) selecting a subset of said set of oligonucleotides of step d) having a desired level of physical, chemical or biological activity.

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99. (Amended) A method of defining a set of compounds comprising:

B8 SUC C7 evaluating *in silico* a plurality of virtual compounds according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically synthesizing a plurality of synthetic compounds corresponding to said plurality of virtual compounds.

100. (Amended) A method of generating a set of oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating *in silico* a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides.

101. (Amended) A method of preparing oligonucleotides comprising:

evaluating *in silico* a plurality of virtual oligonucleotides according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

robotically synthesizing a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides.

102. (Amended) A method of preparing oligonucleotides comprising:

a) generating a library of nucleobase sequences *in silico* according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence;

b) evaluating in silico a plurality of virtual oligonucleotides having the nucleobase sequences of a) according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence; and

B8 c) robotically synthesizing a plurality of synthetic oligonucleotides corresponding to at least some of said virtual oligonucleotides.

REMARKS

Claims 55-103 were pending in the present application. Claims 88-98 and 103, asserted in the Office Action to be directed to an invention that is independent or distinct from the invention originally claimed, have been cancelled without prejudice to their presentation in another application. In addition, claims 57 and 73 have also been cancelled without prejudice to their presentation in

another application. Claims 55, 56, 58-60, 62-67, 69-72, 74, 75, 78-82, 85-87 and 99-102 have been amended herein, support for which can be found throughout the specification. Upon entry of the present Amendment, claims 55, 56, 58-72, 74-87 and 99-102 will be pending.

As a preliminary matter, Applicants acknowledge receipt of the "Attachment for PTO-948" outlining changes for prosecution of applications containing drawings. Formal drawings have been filed on date even herewith under separate cover to the Draftsperson.

I. The Claims Are Clear And Definite

Claims 55-87 and 99-102 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Applicants respectfully request reconsideration in view of the amended claims.

The Office Action asserts that the claims are vague and indefinite because the preambles direct the claim practice to modulation of expression or antisense practice whereas none of the steps of the claims are limited to either of these practices. Claims 55, 56, 58-60, 62-67, 69-71, 99 and 100 have been amended to delete the allegedly confusing language of the preamble. Claims reciting methods of identifying one or more nucleic acid sequences amenable to antisense binding of an oligonucleotide to nucleic acid sequences (*i.e.*, claims 72 and 74-87) are clear and definite. Each of these claims, in fact, recites at least one step whereby a plurality of synthetic oligonucleotides corresponding to least some of said virtual oligonucleotides for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay. Each of these assays provides results that correspond to antisense binding of an oligonucleotide to nucleic acid sequences. Claims 101 and 102 have been amended to recite methods of "preparing oligonucleotides."

The Office Action also asserts that some of the claims recite that the virtual compounds are selected by some undefined "defined criteria." Although Applicants maintain that the claims are clear and definite as drafted, solely to advance prosecution of the present application, Applicants

have amended claims 55, 56, 58, 60, 62-67, 70-72, 74, 75, 79, 80, 82, 86, 87, 100 and 102 to recite the "defined criteria."

In view of the foregoing, all pending claims are clear and definite and persons of ordinary skill would have no difficulty in determining whether a particular method having particular steps is within the scope of the claims. Thus, the claims are definite within the meaning of § 112. *In re Mercier*, 185 U.S.P.Q. 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one skilled in the art can determine what subject matter is or is not within the scope of the claims). Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

II. The Claimed Inventions Are Not Obvious

Claims 55-87 and 99-102 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the combination of U.S. Patent No. 5,463,564 (hereinafter, the "Agrafiotis reference"), Uhlmann *et al.*, *Chem. Rev.*, **1990**, *90*, 543-584 (hereinafter, the "Uhlmann reference") and U.S. Patent No. 5,639,603 (hereinafter, the "Dower reference") taken further in view of U.S. Patent No. 5,720,923 (hereinafter, the "Haff reference") or U.S. Patent No. 5,650,122 (hereinafter, the "Harris reference"). The Office Action asserts that it would have been *prima facie* obvious for one skilled in the art to perform the desired compound design via the Agrafiotis and Uhlmann references and synthesize the compounds via the Dower reference and then perform the assays as desired using the Haff an/or Harris references. Applicants traverse the rejection and respectfully request reconsideration because even if there is sufficient motivation to combine the cited references (and Applicants maintain that there is not sufficient motivation to combine the cited references),the combination of the cited references does not produce Applicants' claimed inventions.

Although Applicants disagree with the assertions in the Office Action as they may pertain to claims 57 and 73, solely to advance prosecution of the present application, claims 57 and 73 have been cancelled without prejudice to their presentation in another application. The remaining claims all recite "generating *in silico* virtual compounds," "evaluating *in silico* a plurality of virtual compounds," "generating a library of nucleobase sequences *in silico*," "evaluating *in silico* a

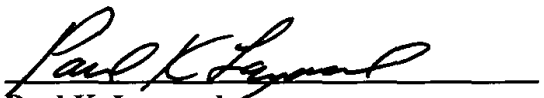
plurality of virtual compounds," or similar language, "according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence." The Office Action fails to assert that the combination of references teaches the steps described above, let alone identify any portions of the references that would support such a conclusion.

In view of the foregoing, the claimed inventions are not obvious in view of the combination of the cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

III. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 564-8906 if there are any questions regarding Applicants' claimed invention. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,



Paul K. Legaard
Registration No. **38,534**

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WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439